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Clinical Proceedings

of the

CHILDREN'S HOSPITAL

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SHOULD VITAMIN D BE GIVEN ONLY TO INFANTS?

VITAMIN D has been so successful in preventing rickets during infancy that there has been little emphasis on continuing its use after the second year.

But now a careful histologic study has been made which reveals a startlingly high incidence of rickets in children 2 to 14 years old. Follis, Jackson, Eliot, and Park* report that postmortem examination of 230 children of this age group showed the total prevalence of rickets to be 46.5%.

Rachitic changes were present as late as the fourteenth year, and the incidence was higher among children dying from acute disease than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of rickets, such as we found in many of our children, interfere with health and development, but our studies as a whole afford reason to prolong administration of vitamin D to the age limit of our study, the fourteenth year, and especially indicate the necessity to suspect and to take the necessary measures to guard against rickets in sick children."

*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in children between two and fourteen years of age, Am. J. Dis. Child. 66:1-11, July 1943.

MEAD'S Oleum Percomorphum With Other Fish-Liver Oils and Viosterol is a potent source of vitamins A and D, which is well taken by older children because it can be given in small dosage or capsule form. This ease of administration favors continued year-round use, including periods of illness.

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PENICILLIN BY MOUTH*

Report of a Clinical Trial

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The advantages of the oral route of administration of Penicillin are obvious and require little elaboration when compared with the parenteral methods. Because of the rapid rate of excretion in the urine, frequent intramuscular or intravenous injections of penicillin are required to maintain therapeutic concentrations in the blood. The inconvenience of such a regimen both to the patient and to the hospital personnel are manifest. Continuous intravenous infusions maintain a more constant serum level but close supervision is necessary and the incidence of thromboses is large enough to make the intramuscular route preferable. Furthermore, hospitalization is usually mandatory for the treatment of infections susceptible to penicillin when the parenteral route is employed.

Consideration of these difficulties has stimulated investigation of methods of prolonging therapeutic blood levels so that less frequent injections will be required. Towards this end, production of a kidney excretory blockade by diodrast[1] or para-amino hippuric acid[2] has been tried but does not seem practical for routine use. Similarly the combination of penicillin in a 3 per cent beeswax-peanut oil suspension[3] for intramuscular use, as well as preliminary chilling of the muscle[4], has been employed to secure prolongation of therapeutic blood levels by decreasing the rate of absorption from the site of injection. In a preliminary report we demonstrated that adequate blood concentrations of penicillin could be obtained when penicillin is given by mouth.[5] Several other reports employing various technics for oral administration have appeared in the recent literature; these include combination of the drug with mild antacids[6] or suspension in oils[7] or raw egg solutions.[8]

The following report represents a preliminary clinical trial of the efficacy of penicillin when given by the oral route:

* Summary of a paper which appeared in the J. A. M. A. **129:** 327 (Sept. 29) 1945.

Permission to reprint this article was granted by the editors of the J. A. M. A.
Presented at the Clinical Conference, Children's Hospital, Washington, D. C., July 10, 1945.

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Methods and Materials

To avoid inactivation, penicillin when given by mouth must escape the destructive influence of gastric acidity and be absorbed from the small bowel before meeting the inhibitory action of Escherichia coli.

For the purpose of these experiments the contents of an ampule containing 100,000 units of powered sodium penicillin was transferred to a plain gelatin capsule (No. 1), which was moistened and sealed and in turn placed in a second capsule of the next larger size (No. 0). Hardening of the capsule containing the penicillin was then accomplished by placing it in solution of formaldehyde U.S.P. diluted 1:20 for five seconds, followed by immersion in 95 per cent alcohol for five minutes. The purpose of the double capsule was to provide additional mechanical protection for the penicillin in its passage through the stomach. Two aluminum hydroxide tablets were given one-half hour prior to the ingestion of each penicillin capsule in order to neutralize the hydrochloric acid in the stomach.

From preliminary experiments[5] the impression was gained that slightly higher penicillin blood levels were obtained when the capsules were taken on an empty stomach. In the clinical trials herein reported, a light diet with low fat content and moderate fluid intake was employed routinely. A three hour schedule of administration of the drug was followed, with slight adjustment of the diet schedule so that at no time was the penicillin capsule administered simultaneously with meals.

The subjects selected for these clinical trials included 14 children ranging in age from 2 to 11 years. There were 10 cases of gonorrhea, 2 cases of broncho-pneumonia and 2 cases of cellulitis. Gonorrhea was praticularly well suited for a clinical trial of the efficacy of the oral administration of oral penicillin because of readily demonstrable bacteriologic evidence of cure.

In cases in which penicillin assays were done while under treatment, samples of venous blood were taken at the end of one-half, one, two and three hours. Also, in 7 instances, penicillin levels were assayed during a consecutive six hour period to demonstrate the incremental rise in the blood penicillin concentration resulting from the ingestion of a second capsule three hours after the first dose.

Penicillin content was determined according to the method of Rammelkamp,[9] using beta hemolytic streptococcus 203 as the indicator organism. Blood samples after withdrawl were immediately placed in the icebox and usually run within two to three days. It is advisable to assay the blood sample for penicillin content as soon as possible, since a certain amount of destruction occurs on standing, thus vitiating the accuracy of the level.

A characteristic of the curves obtained in patients under treatment after the oral administration of 100,000 units in a double capsule, was the rela-

tively rapid appearance of large amounts of penicillin in the blood stream. In the majority of instances the highest titers were observed in the first 30 to 90 minutes after ingestion indicating a prompt absorption from the small bowel. Subsequent levels showed decreasing amounts during the next two hours. A feature common to all the curves was the continued presence of therapeutic serum levels of penicillin three hours after the ingestion of a 100,000 unit capsule. The ingestion of a second 100,000 unit capsule produced an incremental curve in the penicillin titer similar to the initial three hour curve. (Chart 1). It may be concluded that when these capsules are administered every three hours, therapeutic concentrations can be maintained constantly throughout the course of the treatment for all susceptible infections.

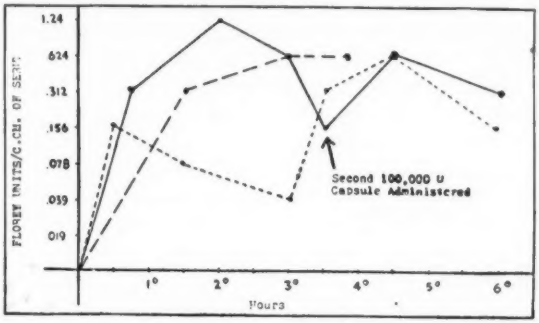

CHART 1.—Illustrating the penicillin blood levels after ingestion of a 100,000 unit capsule and the increment obtained when a second 100,000 unit capsule is given at three hours.

Rammelkamp and Keefer[10] found that the degree of antibacterial action was in direct proportion to the concentration of penicillin in the serum and found the maximum effects against Streptococcus hemolyticus to be in concentration of from 0.019 to 0.156 Florey units per cubic centimeter of serum. Against staphylococci slightly higher levels were necessary, at least 0.156 Florey units being required for maximun effect. Gonococci and pneumococci are both rated as highly susceptible organisms.

A comparison between the penicillin levels in children and adults observed after the oral administration of 100,000 units in a capsule reveals no especial difference. Interestingly, the curves noted in the two groups were similar in regard to concentration and prolongation. Adequate explanation for this observation is lacking, since theoretically one might expect higher and longer sustained levels in children if the dosage of oral penicillin could be calculated on the basis of weight. Further investigation is contemplated to establish the optimal dose by this method in both age groups.

In none of the cases included in this report were any objective or subjective symptoms of toxicity noted even after these relatively large doses. In one case, not included in this series, a total dose of 11,500,000 units was given over a period of fourteen days without toxic effect.

This method of administering penicillin has a wide range of applicability, especially in older children and adults. However, in some of the younger children it was necessary to place the capsule in the esophagus because of their inability to swallow the capsules spontaneously.

Clinical Trials

Gonorrhea: Many reports have appeared in the recent literature concerning the efficiency of penicillin in the treatment of gonorrhea in adults. Observations on the value of penicillin for the treatment of this infection in children have been less numerous but equally satisfactory. There is general agreement that this drug is the most efficacious single agent for the management of this disease. It is curative for sulfonamide resistant strains of gonococci and has the additional virtue of being relatively non-toxic.

The current mode of administering penicillin by the parenteral route complicates the management of an otherwise ambulatory disease. The development of an adequate method of giving the drug by mouth has particular merit in the treatment of this and many other ambulatory infections, since it makes possible its management in office practice. Details of the treatment of 9 cases of gonococcic vaginitis and 1 case of gonococcic urethritis in children ranging in age from 2 to 9 years are presented in the accompanying table. (Table 1)

In view of the well known unreliability of smears alone as diagnostic criteria of gonorrhea, all the cases showed both positive smears and cultures before institution of therapy. Clinical cure does not necessarily coincide with bacteriologic cure; the criterion employed was at least four negative smears and cultures obtained over a period of from three to four weeks after termination of treatment. The adequacy of this observation period is in agreement with the report of Lapenta and his associates.[11] These investigators noted in their observations of 113 cases of gonococcic urethritis treated with intramuscularly administered penicillin that not a single relapse occurred in a three month follow-up when three negative cultures were obtained over a period of twenty-one days.

The therapeutic index of this infection is directly proportional to several factors, viz. the sensitivity of the particular strain of gonococcus to penicillin, the duration of symptoms prior to starting treatment and the extent of the infection. In this regard there is a lack of unanimity of opinion in the literature regarding the optimal dosage of parenterally administered penicillin in the treatment of gonorrhea. Mahoney and his associates[12]

report only 74 per cent of cures after administration of 150,000 units intramuscularly. Lapenta[11] reported 70 per cent cures with 100,000 units. These figures do not coincide with the greater percentage of cures reported by several other investigators who administered 50,000 to 100,000 units.[12,13]

In preliminary attempts to standardize the oral dosage required for gonorrhea, the first 2 patients treated were given 100,000 units at three hour intervals for two doses. However, this dosage failed to effect a cure. Three days later these 2 patients received 100,000 units for three doses and were cured. Similarly, the next patient was given three doses of 100,000 units, following which three negative vaginal smears and cultures were obtained. She was then discharged from the hospital but, ten days later, a follow-up smear and culture proved to be positive and a second course of oral penicillin consisting of 100,000 units every three hours for four doses was given with successful results. Following these preliminary reversals, it was clear that either the total dose of penicillin administered was insufficient or that treatment should have been continued for a longer time. It was therefore deemed advisable to adopt arbitrarily a schedule consisting of 100,000 unit capsules given at three hour intervals for four doses. After the selection of this regimen no relapses occurred in the subsequent 8 cases.

The minimal dosage of oral penicillin for the treatment of this infection cannot be categorically defined. It is likely that cures could have been effected in the majority of cases with less than 400,000 units, especially if smaller single doses were given for a longer sustained period of treatment. However, it is believed that the employment of a larger dose than is considered necessary for every case would insure against symptomatic cures with the production of chronic carriers and prevent an increase in resistance of the strain of organism to subsequent treatment. It is clear that a much larger series of cases must be treated before any definitive statement can be made regarding the optimal oral dose.

Reference to Chart 1 illustrates the incremental elevations in penicillin titer obtained when a subsequent 100,000 units is given three hours after the initial dose. It may be inferred that similar rises in the penicillin blood levels would be present with each additional three hour dose. From this one may postulate the presence of therapeutic concentrations instant throughout the nine or twelve hour period during which therapy is maintained.

As noted in Table 1 a bacteriologic cure was effected within six to twenty-four hours after the institution of therapy with the majority of cases showing no organisms after twelve hours. Although the cures reported here deal with gonorrhea in children the employment of the same schedule of 100,000 unit capsules given every three hours for four doses will probably

TABLE 1

Details of Treatment

CASE	SEX	RACE	AGE	INDIVIDUAL DOSE OF ORAL PENICILLIN	DOSAGE SCHEDULE	TOTAL DOSE	INTERVAL BEFORE NEGATIVE CULTURE	DAYS NEGATIVE	COMMENT
			years	*units*		*units*	*hours*		
1	♀	W	4	100,000	Every 3 hours	300,000	12	4	Failed to respond to 200,000 units; subsequently cured with 300,000 units; 4 negative smears and cultures; no further clinic visits after discharge
2	♂	N	6	100,000	Every 3 hours	300,000	12	74	Failed to respond to 200,000 units; subsequently cured with 300,000 units; 6 negative smears and cultures
3	♀	N	8	100,000	Every 3 hours	400,000	12	35	Relapse after 300,000 units; subsequently cured with 400,000 units; 5 negative smears and cultures
4	♀	N	4	100,000	Every 3 hours	400,000	24	48	Cured: 9 negative smears and cultures
5	♀	N	3	100,000	Every 3 hours	400,000	12	40	Cured: 8 negative smears and cultures
6	♀	N	3	100,000	Every 3 hours	400,000	12	28	Cured: 5 negative smears and cultures
7	♀	N	9	100,000	Every 3 hours	400,000	12	66	Cured: 6 negative smears and cultures
8	♀	N	2	100,000	Every 3 hours	400,000	12	36	Cured: 6 negative smears and cultures
9	♀	W	7	100,000	Every 3 hours	400,000	12	26	Cured: 6 negative smears and cultures
10	♀	N	3	100,000	Every 3 hours	400,000	6	24	Cured: 4 negative smears and cultures

be similarly efficacious in adults. However, this remains to be proved by a clinical trial.

Pneumonia: Two cases of pneumonia were treated by the oral administration of penicillin. Case summaries follow:

Case 1 (chart 2).—J. B., a Negro girl aged 7 years, was admitted to Children's Hospital with a history of fever, chills and productive cough of six day's duration. Two days after the onset of illness she was seen by her local physician and was given 2 gm.

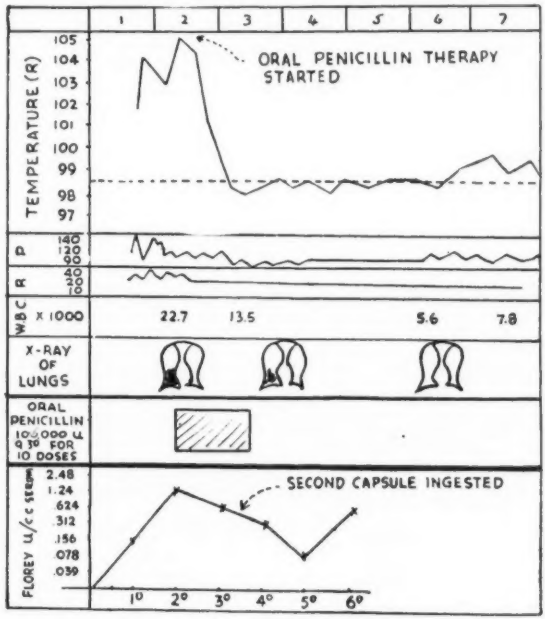

CHART 2.—OBSERVATIONS IN CASE 1

of sulfadiazine a day. Therapy was continued during the subsequent four days without any improvement being noted. On entry into the hospital, sputum examination revealed pneumococcus type XIV, and an x-ray of the chest confirmed the clinical impression of right lower lobe pneumonia. Blood culture was negative. Oral penicillin therapy was started and consisted of 100,000 unit capsules every three hours for ten doses, totaling 1,000,000 units.

Twelve hours after the initiation of treatment, her temperature dropped precipitously from 105 F. to 98.4 F. and she remained afebrile during the remainder of her hospital stay. This was followed by clinical evidence of resolution of the pneumonic process during the next two to three days. A chest film taken three days after termination of therapy was negative. Likewise the white blood cell count dropped

from an initial 23,000 on entry to 5,400 within two days, and pneumococcus organisms were no longer demonstrable in the sputum after forty-eight hours.

Six samples of blood were taken over a consecutive six hour period while the patient was under treatment and assayed for penicillin content. As may be noted in chart 2, adequate amounts of the drug promptly appeared in the peripheral blood after the ingestion of the capsule and was maintained for three hours. When the second capsule was taken at the end of three hours, therapeutic concentrations were maintained and prolonged for another three hour period. The amounts present ranged between 0.078 and 1.24 Florey units per cubic centimeter during this interval.

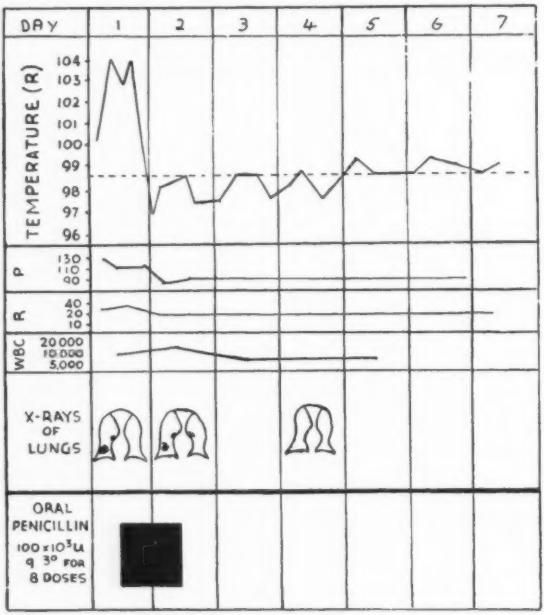

CHART 3.—OBSERVATIONS IN CASE 2

Case 2 (chart 3).—R. H., a Negro boy aged 7½ years, was admitted with the chief complaints of abdominal pain and fever. The temperature on admission was 100.4 F., rising four hours later to 104 F. Pronounced dyspnea, with splinting of the right side of the thorax, was noted. Examination of the chest revealed dulness on percussion, crepitant rales and diminished breath sounds over the right lower lobe. X-ray examination showed an infiltrative lesion in the right base indicative of pneumonia. Two sputum cultures showed Staphylococcus aureus hemolyticus.

The patient was given 100,000 units of penicillin orally every three hours for eight doses, totaling 800,000 units, with a defervescence of fever from 103.8 F. to 97.4 F. twelve hours after the initiation of therapy. The temperature remained normal, with resolution of clinical and x-ray signs in three days (chart 3).

Further trials of oral penicillin therapy for the treatment of pneumonia are now under way. As in the management of gonorrhea, the establishment of an optimal oral dose necessitates an extensive clinical evaluation. In the reported 2 cases, 800,000 and 1,000,000 units given over a period of twenty-four and thirty hours produced a rapid response and cure.

Cellulitis: Two cases of cellulitis of the face were treated with oral penicillin. One patient, a boy aged 11 years, had an extensive involvement of the left side of his face and neck secondary to an infected tooth. He was given 100,000 unit capsules every three hours for twelve doses and showed a prompt effective response, with rapid subsidence of inflammation and swelling in forty-eight hours. The second patient, a child aged 7 years, who had periorbital cellulitis associated with suppurative ethmoiditis, also received a thirty-six hour course of oral penicillin consisting of 100,000 units, every three hours. A similar prompt recovery ensued forty-eight hours after the initiation of therapy.

Conclusions

1. Adequate therapeutic blood concentrations of penicillin after oral administration can be obtained when the drug is protected against inactivation by gastric acidity. A method of providing this protection by the use of a double gelatin capsule hardened by formal dehyde-alcohol immersion together with preliminary neutralization of the hydrochloric acid in the stomach was adopted.

2. Administration of a 100,000 unit capsule every three hours by this method provides constant therapeutic penicillin levels well within or above the effective antibacterial range of most susceptible organisms throughout the course of treatment.

3. A clinical trial of this method on 10 children with gonorrhea, 2 with pneumonia and 2 with cellulitis resulted in prompt recovery.

4. The relatively large doses of penicillin employed produced no toxic manifestations.

REFERENCES

(1) Rammelkamp, C. H., and Bradley, S. E.: Excretion of Penicillin in Man. Proc. Soc. Exper. Biol. & Med. **53:** 30 (March) 1943.

(2) Beyer, K. H., Woodward, R., Peters, L., Verwey, W. F., and Mittis, P. A.: Prolongation of Penicillin Retention in Body by Means of Para-Amino Hippuric Acid. Science **100:** 107 (Aug. 4) 1944.

(3) Romansky, M. J., and Rittman, G. E.: Penicillin: Prolonged Action of Beeswax-Peanut Oil Mixture. Bull. U. S. Army M. Dept., October 1944, No. 81, p. 43.

(4) Trumper, M., and Hutter, A. M.: Prolonging Effective Pencillin Action. Science **100:** 432 (Nov.) 1944.

(5) Burke, F. G., Ross, S., and Strauss, C.: Oral Administration of Penicillin: Preliminary Report. J. A. M. A. **128:** 83 (May 12) 1945.

(6) Gyorgy, P., Vandergrift, H. N., Elias, W., Colio, L. G., Barry, F. M., and Pilcher, J. D.: Administration of Penicillin by Mouth: Preliminary Report. J. A. M. A. **127:** 639 (March 17) 1945.

(7) Libby, R. L.: Oral Administration of Penicillin in Oil. Science **101:** 178 (Feb. 16) 1945.

(8) Little, C. J., and Lumb, G.: Penicillin by Mouth. Lancet **1:** 203 (Feb.) 1945.

(9) Rammelkamp, C. H.: A Method of Determining the Concentration of Penicillin in Body Fluids and Exudates. Proc. Soc. Exper. Biol. & Med. **51:** 95 (Oct.) 1942.

(10) Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus. J. Clin. Investigation **22:** 649 (Sept.) 1943.

(11) Lapenta, R. G., Weckstein, A. M., and Sarnoff, H.: The Inadequacy of a Standardized Dosage of Penicillin in the Treatment of Gonococcic Urethritis. J. A. M. A. **128:** 168 (May) 1945.

(12) Mahoney, J. F., Ferguson, C., Buchholtz, M., and Van Slyke, C. J.: Am. J. Syph. Gonor. & Ven. Dis. **27:** 525 (Nov.) 1943.

(13) Craig, W. M., Thompson, G. J., Hutter, A. M., Barksdale, E. E., Pfeiffer, C. C., and Woolley, P. V., Jr.: Penicillin: A Progress Report. U. S. Nav. M. Bull. **44:** 453 (March) 1945. Fox, H. J.: Penicillin Program at the United States Naval Hospital, Portsmouth, Va.: Observations and Results. War Med. **7:** 170 (March) 1945. Dunfield, V. M., and Mandel, A.: Pencillin—The Rapidity of Its Effect in the Treatment of Gonorrhea. New York State J. Med. **45:** 614 (March) 1945. Neilson, A. W.; Chard, F. H., Hanchett, L. J., Ayers, E., Stepita, C. T., and Rodriquez, J.: Pencillin in the Treatment of Syphilis and Gonorrhea. South. M. J. **38:** 204 (March)1945.

CRYPTORCHIDISM*

Dr. James E. Loggins, Jr.

Cryptorchidism is defined as a condition in which one or both testes fail to enter the scrotum. There has been existent for the past several years a wide divergence of opinion regarding therapy of this condition. This summary of the current literature is an attempt to assay the most desirable and successful method of managing these cases.

Mechanism of Descent. Anatomically, there are two types of cryptorchidism; those that are in the normal pathway of descent but which have not reached the scrotum, and those that have deviated from the usual tract and are therefore ectopic in position. The testes originates in the abdominal cavity at the level of the tenth thoracic vertebra from a central mass of epithelium. Descent normally is in the following chronological order: (1) third month—from the lumbar region into the iliac fossa; (2) fourth to seventh month—remains at the internal inguinal ring; (3) seventh month—through the inguinal canal; (4) eighth month—at the external inguinal ring; (5) ninth month—enters the scrotum. Descent may be interrupted at any point giving rise to cryptorchidism[1]. This process was first believed to be due to contractions of the gubernaculum testes, a fibro-muscular band. The gubernaculum is attached superiorly to the testis and inferiorly splits into five tails which attach to the region of the inguinal ligament medial to the anterior superior iliac crest, the anterior aspect of the pubis, the femoral or Scarpa's triangle, the perineum beneath the Colles fascia, and the process vaginalis. It is this last attachment which has been thought to play the major role. Interestingly, the attachment is not to the scrotum itself but rather to the process vaginalis, an evaginated portion of peritoneum. According to Bronan, the gubernaculum shortens, particularly during the seventh month, drawing the testes into the scrotum. Opposed to this view is the fact that the testes descends before the gubernacular muscle fibers develop, and also, at operation the testis may be drawn from the sac without pulling on the scrotum, hence there is no apparent tractive force[1]. Hunter believes the undescended testicle is an imperfect organ and therefore did not migrate in a normal manner; a normal testis, if it did not meet anatomic barriers, would always reach its normal habitus in the scrotum. Opposed is Sir Astley Cooper's view that the cryptorchid testis is normal in structure but not completely developed; the scrotal temperature is absolutely necessary for complete development

* This paper was submitted in competition for the Mead Johnson Pediatric Essay Awards given to Georgetown and George Washington fourth year medical students.

of spermiogenesis and maldevelopment, hence is the result and not the cause of maldescent.[1]

Classification. Etiologically there are three types of mal-descent; upon the differentiation depends the therapy to be employed.

1. Those cases in which there are structural changes or malformation of the pathway, preventing further testicular descent.
2. Those cases in which the testis has deviated from the pathway and are ectopic.
3. Those cases in which there is a disturbance in the hormonal mechanisms involved.

Ectopic testes occupy positions comparable to the attachments of the gubernacular tails and hence there are four types most frequently found: femoral, perineal, pubic, and those in the region of the inguinal ligament near the anterior superior iliac spine.

Although no one endocrine organ may be singled out in any hormonal dysfunction, these cases are primarily involved with the anterior pituitary gland and with the testicle. The anterior pituitary secretes in the male the counterpart of Prolan A and Prolan B which are present in the female. The Prolan A or follicle stimulating hormone stimulates spermiogenesis, while Prolan B or luteinizing hormones stimulates the interstitial cells of the testis which then produce testosterone.[2] It is believed to be testosterone which activates the process of descent. With the above in mind, it is easy to understand the major hormonal disturbances which are present in cryptorchidism. These include: (1) hypopituitarism in which there is insufficient Prolan B to activate the testis; (2) primary hypogonadism where there is an inadequate reaction to pituitary stimulation, and (3) hypothyroidism in which there is a failure of primary tissue differentiation and a lack of testicular response.

Diagnosis. The diagnosis of cryptorchidism is demanding of an accurate history and careful physical examination. Frequently the pseudocryptorchid testis is confused in diagnosis. The differentiation is important as they do not require treatment. The family should be questioned regarding the testis to determine if at any time it has been present in the scrotum. If it has, then it is classified as migratory or pseudocryptorchid. A migratory testis may travel from the scrotal sac to the mid inguinal canal and return.[3] If the testicle is in the sac but high, it is also classified as migratory. The patient should be examined on at least two separate days in the standing position to eliminate pseudocryptorchid cases. Sometimes the testis may be caused to descend if external heat is applied to the scrotum. If there has never been descent, the scrotum is flat and band-like, rather than sac-like.

Treatment. In considering therapy, we enter the most controversial

portion of cryptorchidism. Intervention in cryptorchid cases is indicated for the following reasons. A testis does not function normally either in spermiogenesis or in production of testosterone, if it does not enter the scrotum; it is more liable to traumatic derangement such as torsion or direct trauma; malignancy is more frequent, and cosmetically and psychically it is more desirable to have the testes in the scrotum for their absence frequently produces personality changes, particularly as puberty approaches.[4]

At puberty, the cryptorchid testis shows demonstrable atrophy, most marked in the spermatogenic tissue.[3] This is seldom seen before puberty but the clinical results of Thompson, and of Rankin, indicate that the earlier therapy is instituted, the better are the chances for a normal sized, functioning testicle. Rankin advocates the fifth year of life as an optimal age.[5] Thompson believes any time before puberty is satisfactory but an early age is desirable.[2] Some cases correct themselves during puberty without treatment of any type and on this basis Cone advocates waiting until well into puberty to begin treatment.[6] However, this method sacrifices the vast majority of testes.

Surgical Management. There are several methods for surgical management. All of these procedures have in common the lengthening of the cord and freeing of any adhesions, permitting the testis to be brought into the sac. The variations are concerned with retaining the testis in position and preventing retraction at a later date. These methods include: (1) narrowing the neck of the scrotum by sutures to prevent retraction, (2) suturing the testis to the scrotum, (3) drawing the testis by suture, wire, or elastic, to some fixed point outside the scrotum, (4) transplanting the testis to the opposite scrotal sac, using the scrotal raphe to prevent retraction, (5) multiple stage procedure, fixing the testis to the posterior wall of the inguinal canal, or (6) fixation of the testis to the thigh (Keetley-Torek). The most satisfactory procedure is the operation described separately by Keetley and by Torek in which the testis is placed in the sac, the sac incised at the lower border, the testis sutured to the thigh and the sac sutured over this. In six weeks the testicle is freed and the scrotum closed. Retraction after this operation is unusual.

Hormonal Therapy. The mechanism of this type of treatment is the replacing of a deficiency of testosterone, either by stimulating the testes to production or by introducing the testicular hormone itself.[2] There are several preparations available for use in this condition including: (1) extract of the anterior pituitary gland; (2) pregnant mare's urine, high in equine gonadotropin; (3) pregnant human serum; (4) chorionic gonadotropin and (5) testosterone preparations. The first two listed are variable and hence produce unpredictable results and may stimulate anti-hormone production;

they contain both the follicle and lutenizing hormones.[2] Chorionic gonadotropin which contains the lutenizing element only, and which is prepared from human placental tissue, has been used most successfully. Stimulation therapy should be first tried, and if the testis is not caused to descend, then the use of testosterone preparations may be of some help. Therapy may be started with 500 I.U. of chorionic gonadotropin two to three times a week and continued until descent or until it is established there will be no effect. A total of 10,000 I.U. of gonadotropin is sufficient to indicate the result. Testosterone propionate, 25 to 50 mgms. twice a week, or methyl testosterone, 30 to 90 mgms., may be given, the latter orally, although the results with these replacement preparations are disappointing.

The harmful effects of hormonal therapy have caused many workers to avoid this type of treatment.[8] These effects are:

1. Excessive genital growth—During therapy the genitals increase in size and puberty praecox may result. This is easily controlled by frequent observation of the patient during treatment. The drug should be discontinued if the growth becomes excessive. However, this effect is only temporary and size recedes with cessation of therapy.[2]
2. Early cessation of testicular function—There is an azoospermia during treatment but recovery follows omission of therapy in sixty days.[8]
3. Early epiphyseal closure—This is controversial. Dorff has shown quite to the contrary that chorionic gonadotropin is a more effective growth stimulator than is the growth factor of the anterior pituitary gland, and that as long as the epiphyses may be open, growth is stimulated to reach the high age norm. He concludes "normally there is a close relationship between sexual development and linear growth. . . high growth sprints contradict the impression that sexual development and height growth are antagonistic and that gonadal stimulation is therefore not desirable."[9]
4. Symptoms of heart failure—Occurs in old men with arteriosclerosis or hypertensive heart disease. Old age is a contraindication for glandular therapy.
5. Acne Vulgaris—The effect here is temporary.
6. Hypermetabolism—The mechanism is unknown, but the effect is temporary.

There are no harmful effects resulting from hormonal therapy that can not be avoided by careful observation of the patient during the treatment period.

Thompson states: "Careful study of the data available indicates glandular treatment causes descent only of those testes which would descend at

the time of puberty without treatment."[8, 10] Why then should glandular therapy be used at all? Definitely harmful effects result if the condition is allowed to progress until the age of puberty. Glandular treatment makes possible the determination at an early age of mechanical obstruction preventing descent and indicates the need for surgical intervention. Even when ineffective, glandular therapy facilitates surgery by stimulating the involved genitals to an increased size.[11]

Different workers report widely varying results following therapy with chorionic gonadotropin. Harding reports success in 76 per cent of the cases.[3] Goldman obtained complete descent in ten of eleven cases treated.[7] Thompson reports success in 32 per cent of the cases treated under ten years of age, 17 per cent if over sixteen years. He believes these discrepancies in results obtained by various workers are due to the inclusion of pseudocryptorchid cases; his series has excluded these and may be the more accurate.[2]

The best results may be obtained through a combination of medical and surgical treatments. A course of glandular therapy should be employed initially, using chorionic gonadotropin and it is advisable to continue this until the testes descend into the scrotum or until it is shown that there will be no descent. This may be determined in two to six months. If there is no success, surgical intervention is indicated, preferably the Keetley-Torek operation, immediately following the completion of hormonal treatment, so that advantage may be taken of the increased size of the involved parts. It is desirable to institute care before puberty in all cases and if possible any time after five years of age.

Conclusions

1. Treatment of cryptorchidism is advisable to produce a normal sized, functioning testis.

2. A combined glandular and surgical treatment plan probably yields the best results. All cases are first tried on chorionic gonadotropin and if there is not complete descent, then surgical intervention is indicated and employed immediately.

3. Cryptorchism should be corrected before puberty and at an earlier age if possible.

4. Hormonal therapy produces no harmful effects that may not be avoided by careful observation of the patient.

REFERENCES

(1) Iason, A. H.: American Journal of Surgery **65:** 353, 1944.

(2) Thompson, W. O., and Heckel, N. J.: Journal of the American Medical Association **117:** 1953, 1941.

(3) HARDING, F. F.: Journal of Pediatrics **23:** 451, 1943
(4) ABRAHAMSON, R. H.: Journal of Urology **51:** 301, 1944.
(5) RANKIN, L. M., AND EGER, S. A.: American Journal of Surgery **57:** 183, 1942.
(6) CONE, R. E.: Annals of Surgery **119:** 591, 1944.
(7) ABRAHAMSON, R. H.: Archives of Surgery **44:** 170, 1942.
(8) THOMPSON, W. O.: Journal of the American Medical Association **125:** 15, 1944.
(9) DORFF, G. B.: Archives of Pediatrics **59:** 791, 1942.
(10) MOORE, C. R.: Journal of Urology **47:** 31, 1942.
(11) LAPIN, J. H., KLEIN, W., AND GOLDMAN, A.: Journal of Pediatrics **22:** 175, 1943.

NEPHROSIS

Case Report No. 38

Dr. Sidney Ross J. S.—45-3937

J. S., a 2½ year old white male was admitted to Children's Hospital on May 14, 1945 with the chief complaint of edema of the face and extremities. The edema began insidiously about 3 weeks prior to entry. There was no acute infection preceding the onset of the edema. No dysuria or hematuria was observed at any time since the onset of the current illness. The patient had experienced no headaches, drowsiness or vomiting, had remained active and playful and at no time had any elevation in temperature been observed. The past history and family history were noncontributory.

Physical examination revealed a well developed, well nourished white male who did not appear acutely ill. There was noticeable edema about the eyelids together with some localized infraorbital swelling. Fundoscopic examination revealed no hemorrhages or exudates. The tonsils were somewhat large and injected. No cervical adnopathy was present. The heart and lungs were negative. On gross inspection the abdomen appeared full with some slight umbilical protrusion; however no shifting dullness nor fluid wave was elicited. There were no abdominal masses palpable. The liver edge was felt about one centimeter below the right costal region, but the spleen was not palpable. There was minimal pitting edema of the sacrum and the extremities. Blood pressure was 105/65.

On laboratory examination the hemogram revealed a red cell count of 4,120,000 with 14 gms. of hemoglobin; the white cell count was 5,600 with a differential of 33% neutrophils, 65% lymphocytes and 2% eosinophils. The urinalysis on entry showed 1,000 mgms. of albumin with a specific gravity of 1.030. There was no sugar or acetone present and examination of the urinary sediment revealed only a few white cells. The total protein was 3.45 gms.% with 2.89 gms.% of albumin and .56 gms.% of globulin yielding an A./G. ration of 5.1/1. The blood cholesterol was 190 mgms.% and the NPN was 38 mgms.%.

During the first week following admission the edema became progressively more marked and this was accompanied by a moderate degree of oliguria. The patient's weight, which on entry was 33 pounds, showed a noticeable gain and during the first two weeks in the hospital the child gained 2 pounds. He was maintained on a high protein, high carbohydrate, salt-free diet but his appetite was only fair.

Ten days following entry, the patient was started on concentrated serum albumin and received 170 cc. in divided doses during the next four days. Following initiation of concentrated serum therapy, the patient lost 2 pounds and there was a moderate transient decrease in the severity of the edema. Concomitantly the urinary output during this interval was considerably increased. It was noted at this time that the patient's blood appeared very dark and flowed sluggishly on venipuncture. Simultaneously there appeared an increased number of stools. No febrile response was noted as a result of the serum therapy. Repeat blood chemistries following serum therapy showed an NPN of 46 mgm.%, a cholesterol of 280 mgm.%, and plasma chloride was 495 mgm.%. The total protein had risen to 4.62 gms.% with 2.88 gms.% of albumin and 1.74 gms.% of globulin. (See chart 1.) There was no essential change in the urine except for the appearance of an occasional red cell; the albuminuria continued to range between 1000–2000 mgms.%, and the specific gravity remained approximately 1.030. Three days after termination of serum therapy the edema was noted to have become more severe than at any time since entry. Oliguria became marked and the child gained four pounds within the next four days. During the following week the weight fluctuated between 33 and 35 pounds. On June 4, 1945, another 50 cc. of serum albumin was administered intravenously and this same dose was repeated on the following day. Following this the urinary output showed some increase and during the subsequent week the weight of the patient had become stabilized at about 35 pounds. One week after termination of this second course of serum therapy the total protein was found to be 2.4 gms.% with 2.05 gms.% of albumin and .35 gms.% of globulin with an A/G ratio of 5.8/1. The urine continued to show large amounts of albumin ranging between 1,000 and 2,000 mgms. and there were occasional fine granular casts with white cells noted in the sediment together with the infrequent appearance of an occasional red cell. The blood pressure which on entry was 105/65 remained substantially within normal range throughout the entire hospital course. The patient was discharged on June 29, 1945 after a 45-day hospital stay.

During the next three weeks at home he seemed to be in moderately good health except for the persisting edema and abdominal ascites. During this interval he had been maintained on a high protein low-salt diet and his appetite remained moderately good. However, the edema became more progressive and the child developed some dyspnea and cough. He was re-admitted to the hospital on July 7, 1945, five weeks after his initial discharge.

Physical examination at the time of re-entry to the hospital revealed

marked generalized anasarca involving the eyelids, face, lower extremities and scrotum. The abdomen was markedly distended, a fluid wave and shifting dullness being readily elicited. The child appeared somewhat dyspneic. Blood pressure was 100/60, temperature 100°.

Hemogram revealed a hemoglobin of 8.5 gms. with 2,500,000 red cells;

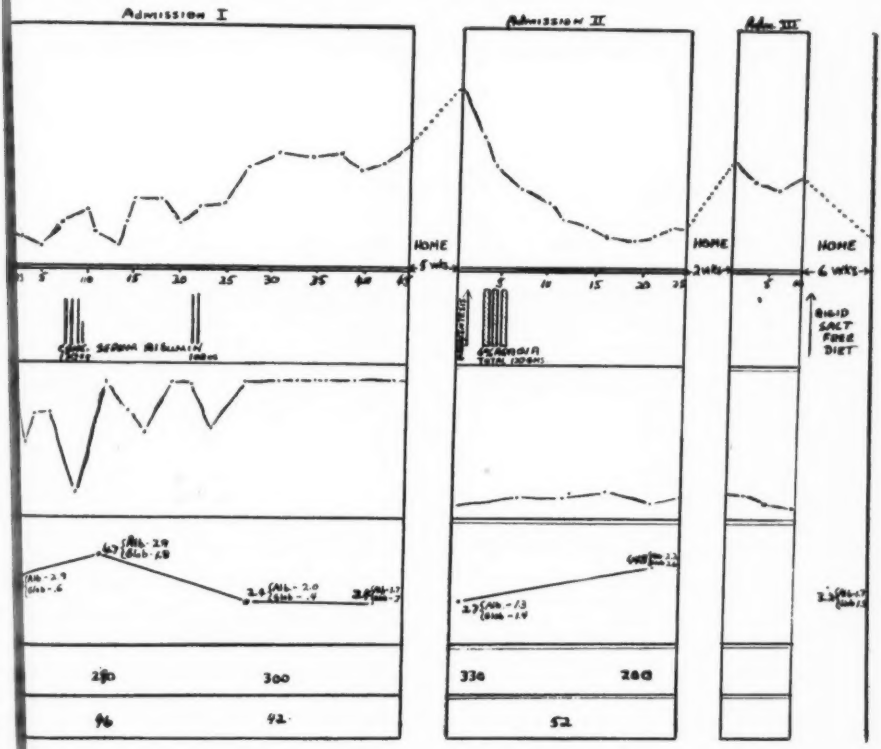

Chart 1, Summary of Case J. S.

the white cell count was 5100 with 58% polys, 39% lymphocytes with 3% eosinophils. Examination of the urine showed 200 mgs. of albumin with fine and coarse granular and hyaline casts and a few white cells. There were no red cells present at this time. Total protein was 2.69 gms.% with 1.29 gms.% of albumin, 1.40 gms. of globulin and an A/G ratio of .9/1. Cephalin flocculation test was negative, and the prothrombin time was 57%

of normal. The blood cholesterol was 330 mgms.% and the NPN was 52 mgms.%.

Three days following entry, a paracentesis was performed and 1500 cc. of straw colored fluid was withdrawn which was sterile on culture.

One week after hospitalization the child was started on acacia which was administered as a constant intravenous drip and during the next two days he received a total of 120 grams of acacia. Following the institution of this therapy a diuresis occurred and during the next 12 days the weight dropped from 43 pounds to 33 pounds, leveled off, and then maintained itself at approximately 34 pounds during the next week. Coincident with the administration of acacia, the temperature rose to 103° and came down by lysis upon termination of acacia therapy.

Following discharge the patient was maintained on a daily intake of between 40 and 50 gms. of protein and a chart maintained by the parents showed the urinary output to be approximately 50 to 75% of the fluid intake.

He was re-admitted to the hospital on September 4, 1945 because of fever. Temperature was 101° on entry. He did not appear acutely ill and except for the slight increase in the extent of the anasarca, the physical examination was otherwise negative.

A hemogram at this time showed 10 gms. of hemoglobin with 4,000,000 red cells. The white cell count and differential were essentially within normal limits. Urinalysis at this time showed numerous red cells, occasional white cells and 400 mgms. of albumin. Cholesterol was 265 mgms.% and the total protein was 2.87 gms.% with 1.44 gms.% of albumin and 1.3 gms.% of globulin. The A/G ratio was 1.1. The temperature came down on the day following entry and his condition remained essentially unchanged during the subsequent week of hospitalization.

After consultation with Dr. Lee Farr of the Naval Medical Center, Bethesda, Maryland, the child was placed on a rigidly salt-free diet containing less than 0.5 grams salt a day. This diet has been strictly observed by the parents who are exceptionally intelligent and cooperative.

During the past two months, the patient has been followed in the Dispensary, and except for transient fluctuations of a mild degree, the edema has been minimal. The weight has remained constantly in the neighborhood of 34 to 35 pounds. The child's appetite has been excellent and he has been more active than usual. A moderate anemia manifested itself and he has received two transfusions of whole blood during this interval.

Within the past month, the urine has shown many red blood cells on two occasions, with a persisting albuminuria ranging between 400 to 500 mgm.%. The blood pressure, however, has remained within normal range.

Discussion

Dr. Lee Farr*

Our knowledge concerning the etiology of this disease state is largely speculative. The absence of clear cut factors of causation or progression limits our therapeutic approach. At the present time the aim of therapy is threefold: (1) Control of the renal lesion; (2) Control of malnutrition; (3) Control of acute infectious episodes which usually are the cause of death. Therapy is not influenced by classification as nephrotic type of chronic glomerulonephritis or as so-called "pure" lipoid nephrosis.

As a matter of interest, to me it would appear most likely that this child has the nephrotic type of chronic glomerulonephritis. This is based on the observation that he has had some increase in blood non-protein nitrogen and that he has a significant anemia. In the group which may clinically be classified as nephrosis, we have noted generally a urea clearance above 140 per cent of normal. The corollary of this is that all such patients have a low blood urea nitrogen. This group also shows a normal ability of the kidney to concentrate urine to a non-protein specific gravity of 1.026 or above. Anemia is extremely rare. There seems to be little tendency for progressive destruction of the kidney and death is usually from intercurrent infection. In the nephrotic type of chronic glomerulonephritis, the urea clearance is initially normal or below. Temporary to permanent increases in blood urea nitrogen concentration are noted, anemia is usually present and the concentrating power of the kidney is impaired. Although in the adult I have never seen recovery if marked improvement was not shown within six months of onset, in the child the period which may intervene before improvement starts is considerably greater, possibly as long as two years. Treatment of the two conditions is, as I stated before, identical.

Control of the renal lesion cannot be completely secured. Our efforts in this regard consist mainly in keeping the physiological environment as nearly ideal as possible through a balanced diet and careful attention to prevention of an excess intake of sodium salts. Physical exhaustion should be avoided and it is wise to exclude from the therapeutic armamentarium drugs and preparations which may have nephrotoxic qualities.

Perhaps the greatest hazard to these children are recurrent infections, usually respiratory. When hemolytic streptococci are the causative-agents, renal damage is very likely to follow. Pneumococci are somewhat less dangerous but it should be pointed out that in this group a pneumococcus pharyngitis is not a rarity. Chronic infections of adenoid tissue seem to be peculiarly hazardous and when one encounters such a condition

* Navy Medical Center, Bethesda, Maryland.

the risk of operative procedure is less than ineffective therapy. Transfusions must be carried out with meticulous care to avoid transfusion reactions. Sulfonamide drugs other than sulfanilimide should be given with great caution and penicillin used whenever possible. Acacia must be given with care and consideration for its accumulation in the liver, spleen and kidney on repeated dosages. I have also seen acute uremia follow acacia injection.

Anything which may even temporarily reduce renal blood flow is fraught with danger. We attempt to achieve a maximum flow of blood through the kidney through the stimulating effect of a high protein diet. Shock is particularly dangerous and if such a condition is suspected as developing, it should be vigorously combatted with parenteral therapy.

Control of the malnutrition is somewhat more successful. The depletion of body tissues in these children is largely masked by a great increase in extracellular fluids. This malnutrition is a part of the disease itself and although it seldom can be eliminated, it can be ameliorated. Insofar as we know, metabolism of protein is normal but assimilation of nitrogen by the individual to restore body protein to normal levels is blocked. Excessive protein intakes have not been effective and most consistent results have been obtained with diets containing an amount of protein optimal for the normal child of that age. Thus with a four year old child, it was learned that nitrogen equilibrium was seldom attained with dietary protein less than 2.5 grams per kilogram ideal body weight per day. (Ideal body weight is the expected body weight for a normal child of that age and height.) On the other hand when the dietary protein was increased to above 4 grams per kilogram ideal body weight, there was less actual and relative assimilation of nitrogen. This paradoxical dumping can also be demonstrated in normal children but is less sharply defined than in the nephrotic subject. Approximately twice as many calories should be given as fat than as protein. This top level of nitrogen assimilation can be increased by parenteral administration of protein hydrolysates but a definite system of therapy utilizing this knowledge has not as yet been developed. Since these children usually show roentgen evidence of decalcification, attention should be paid to the calcium intake.

Hand in hand with increased nitrogen intake goes a decreased sodium chloride intake. On the average a child of this age with the nephrotic syndrome cannot excrete more than 0.5 gram of salt per day. To lessen edema it is essential that the salt intake be kept below this level. The difficulties of devising varied and palatable diets within these limits are great, but I believe they are decidedly worth the efforts required. In the great majority of patients we were able to satisfactorily control edema

through salt restriction alone and did not have to depend upon uncertain effects of diuretics.

We now turn to a consideration of the third phase of therapy: The control of acute infectious episodes, almost uniformly pneumococcic peritonitis, which are the common cause of death. These episodes I have termed nephrotic crises. The development of acute peritonitis in these children must be considered as a part of the natural history of the disease and not as a chance, accidental infection serious in its own right. Fortunately in this aspect of therapy we have been quite successful. It is not possible to predict when nephrotic crises will develop but if the plasma albumin falls below 1 gram per 100 ml. plasma or if the plasma amino acid nitrogen concentration drops to between 2.5 and 2.6 milligrams of alpha amino acid nitrogen per 100 ml. of plasma, a crisis is exceedingly likely to develop, suddenly and without further warning. Mortality in these children with pneumococcus peritonitis treated with specific, potent anti-pneumococcus sera is the same as in untreated children, approximately 80 per cent per attack. The crises can be specifically diagnosed by demonstration of a plasma amino acid nitrogen concentration of less than 2.5 milligrams per 100 ml. when the ninhydrin-CO_2 method is used. Treatment must be immediately instituted. In my experience, in every instance protein hydrolysates given intravenously have proved therapeutically effective whether there was heavy bacteremia or not and whether or not specific drugs or sera were used concomitantly. Approximately one gram of protein hydrolysate per kilogram ideal body weight is given intravenously every six hours until the plasma amino acid nitrogen concentration returns to above 2.5 milligrams per 100 ml. This therapy may be supplemented but not supplanted by specific serum or sulfa drug therapy. With the development of penicillin to its present availability, it would seem to be the ideal adjunct but I have not used it in this way personally. Recovery from the episode is by crisis which usually occurs within three days but may occur within a few hours. Over a three year period and through some forty odd crises we had a zero mortality in patients treated in this fashion.

These crises do not seem to have any fundamental effect upon the course of the disease. Repeated episodes do not impair the ultimate prognosis. The danger is immediate and if the patient can be carried through the nephrotic crisis his chances for complete recovery are as good as ever. Now that we can carry a majority of our patients through nephrotic crises, we can begin to acquire knowledge regarding the further natural history of the disease and the chances of a patient for complete recovery.

To return to our patient under discussion, his prognosis is grave. He has, at times, shown an elevation of blood NPN suggesting that there is a strong tendency to progressive destruction of renal tissue and he has developed a severe anemia which is always a danger sign in nephritis. On the

other hand, due to the fact that he is only 3 years old, there is still a possibility of complete recovery if he can be protected against exacerbations of renal and metabolic disorder. It is worth striving for very diligently to see if in this instance the scales can be tipped in a manner which will permit this child to develop into a healthy normal adult.

Dr. Lewis K. Sweet: Have you seen any patients cured following treatment with amino acids? Have you had any experience with oral amino acids? What diuretics are best to use?

Dr. Farr: I have had one patient in whom recovery seemed clearly to follow parenteral amino acid administration. This child had been ill two to three months before admission. She developed a progressively increasing edema which made home care difficult and at the time of admission did not appear unusual. Clinically she could be classified as a pure lipoid nephrosis. She was six years old. Over a ten day interval she received 300 to 400 grams of casein hydrolysate intravenously and within three weeks her plasma albumin had risen from about 1.5 grams to 4.0 grams per 100 ml. plasma. In another month her plasma amino acid concentration had risen to normal. She appeared completely well and still remained so five years later. We did treat five other children intensively. In this group the disease had been present from one to five years before such therapy was begun. No startling immediate effects were noted. Whether or not there was any long term effect, I do not know as I have not had an opportunity to see these patients over the last four years. Oral administration of casein hydrolysate proved ineffective in the treatment of one child in a nephrotic crisis which resulted in death. We did not carry on further studies with oral preparations. I have used mercurial diuretics very seldom. In many instances, showers of casts and red blood cells followed their administration and because of possible harm their use was discontinued. Potassium salts were ineffective. Urea was the diuretic of choice. It is harmless, easily administered in grape juice or grapefruit juice and is effective whenever a diuretic might be expected to be effective.

Dr. Burke: What prognosis can you give a child with nephrosis?

Dr. Farr: I cannot give a reasonable prognosis because deaths in crises have obscured data on the true course of the disease. The mortality rate has been extremely high. Approximately 10 to 15 per cent made recoveries without recurrences for the succeeding three years in the group I studied. With the better therapy available for treatment of nephrotic crises the figure for recovery should rise very substantially.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by Dr. E. Clarence Rice
Assisted by Dr. Robt. B. Sullivan

Held every Tuesday afternoon at 3:00 p.m.

GRANULOSA-THECA CELL TUMOR OF THE OVARY

Case Report No. 39

Dr. Robert B. Sullivan G. J.—43-3210

G. J., a twenty-one month old colored girl, was admitted to Children's Hospital on May 3, 1943 because of vaginal bleeding. She had been in good health until three weeks before admission when a slight white vaginal discharge was first noticed. After a few days this became brown in color and finally bloody. At first the discharge recurred only at four to five day intervals but later there was "spotting" the size of a dime every hour. In every other respect the child seemed completely well.

The birth and development had been normal. She had been well cared for and had had no previous illnesses. The parents and two siblings were in good health.

She was a well-developed well-nourished colored girl appearing in robust health. Her weight was twenty-three pounds and she was thirty-five and one half inches tall. The temperature was normal. Her breasts were slightly enlarged and there was a small amount of pubic hair. An abdominal mass was felt in the lower left quadrant which could be moved to the midline. It was rounded, fairly firm, and measured about six by eight centimeters. On rectal examination the mass could not be palpated and the uterus was thought to be of normal size. The labia were slightly enlarged. Blood pressure was 90/50.

The hemoglobin was 10 grams per cent and the red blood cell count was 3.26 million per cubic millimeter. The white blood cell count and the differential were normal. Routine urinalyses, a Kahn, and a vaginal smear for gonococci were negative. The blood sugar was 72 milligrams per cent, the blood chloride 479 milligrams per cent and the blood cholesterol 130 milligrams per cent. An x-ray of the chest revealed only that both sides of the diaphragm were somewhat elevated. A flat plate of the abdomen, x-rays of the skull, spine and pelvis and an intravenous pyelogram were reported negative. Urine specimens were sent to another laboratory for estimations of estrogenic substances but unfortunately no report was returned.

On the twenty-third hospital day an exploratory laparotomy was per-

formed, the pre-operative diagnosis having been granulosa-cell tumor of the left ovary. Through a low midline incision a large tumor of the left ovary was delivered which measured 10 by 8 by 6 centimeters. It was nodular and firm and the fallopian tube was attached to one side. The central portion of the tumor was yellow-white and encapsulated. There was a rim of light gray-brown tissue around this.

G. J., 21 Months Old Colored Female with a Granulosa Theca Cell Tumor. Note the hypertrophied labia and the enlargement of the breasts.

The microscopic sections were reported by Dr. Janvier W. Lindsay as follows:

"Ovarian tumor: Sections show a densely cellular structure with many cystic spaces varying in size and outline. Most of these spaces are evidently of follicle origin and have a uniform wall of typical granulosa cells which are sharply defined from the surrounding stroma. The stroma is made up of more or less elongated to spindle cells with patches of round or polygonal cells. Some groups of the latter appear to contain fat globules though fat does not seem to be a strikingly large element in this section. The greater part of the tumor is considered to represent a number of theca

cells and the cells of the usual ovarian stroma, and the growth should be classed as a granulosa-theca cell tumor, recognizing Novak's caution against the attempt to differentiate too sharply between these two. It is probably impossible to determine the matter of malignancy on histological or gross characteristics, because of the frequency of recurrence or appearance of "new" tumors in instances considered benign. Diagnosis: Granulosa-theca cell tumor."

Granulosa Theca Cell Tumor of the Ovary

The post-operative course was febrile for one week after which recovery was complete. A follow-up physical examination nineteen months later revealed a healthy child undergoing normal growth and development.

Discussion

There have been about twenty cases of granulosa cell carcinoma reported in the literature occurring in children from nine months to fourteen years of age. The case just presented is the only one recorded at Children's Hospital. In it were elicited most of the classical clinical signs. There was a mass in the lower abdomen or pelvis, hypertrophied mammary glands and labia, growth of pubic hair, and vaginal bleeding. The skeletal growth was precocious since she was one inch taller than the normal maximum for a

girl four month's her senior. Other signs which were not demonstrated in this case were enlargement of the uterine body and cervix, and thickening and cornification of the vaginal epithelium.

A laboratory procedure of considerable importance in making this diagnosis is the demonstration of an increased estrogen content in a twenty-four hour urine specimen. Normal pre-adolescent children usually excrete much less than 1000 international units of estrogenic activity per day. Those with a granulosa cell carcinoma may excrete 100,000 international units per day.

Most of the tumors with endocrine manifestations are readily excluded in the case under discussion. The arrhenoblastoma is a masculinizing growth and no cases have been reported in patients under fifteen years of age. Testicular neoplasms occur only in boys. Neoplasms of the adrenal cortex are masculinizing except for a very few instances in which they have been feminizing, none of which were in the pediatric age group. Pineal tumors with hormonal effects occur only in boys. Tumors of the floor of the third ventricle probably present the greatest diagnostic difficulty. They are characterized by:

1. Precocious homeotypical sexual development.
2. The appearance of secondary sexual characteristics.
3. Excessive somatic development.
4. Advancement in bone age.
5. Water balance disturbances characterized by either polyuria or oliguria.
6. Minimal or no signs of an expanding intracranial lesion.

Encephalograms may demonstrate the tumor in some instances.

The Albright syndrome (multiple bone cysts with areas of pigmentation and sex precocity in girls) could be excluded in this case by the absence of pigmentation and bone lesions and the presence of the abdominal tumor.

The treatment of granulosa cell carcinoma is surgical removal with periodic estimations of the urinary estrogen excretion during the first few postoperative years in order to discover recurrences. Metastases and recurrences are not common and the prognosis is excellent.

BIBLIOGRAPHY

(1) Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndromes characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. New England J. Med. **216:** 727, 1937.

(2) Bland, P. B., and Goldstein, L.: Granulosa Cell and Brenner Tumors of the Ovary. Surg., Gynec. & Obst. **61:** 250, 1935.

(3) Gross, R. E.: Neoplasms producing endocrine disturbances in childhood. Am. J. Dis. Child. **59:** 579, 1940.

(4) Novak, E., and Gray, L. A.: Clinical and Pathological Differentiation of Certain Special Ovarian Tumors: Granulosa Cell Carcinoma, Arrhenoblastoma, Disgerminoma, Brenner Tumor. Am. J. Obst. & Gynec. **31:** 213, 1936.

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Washington, D. C.

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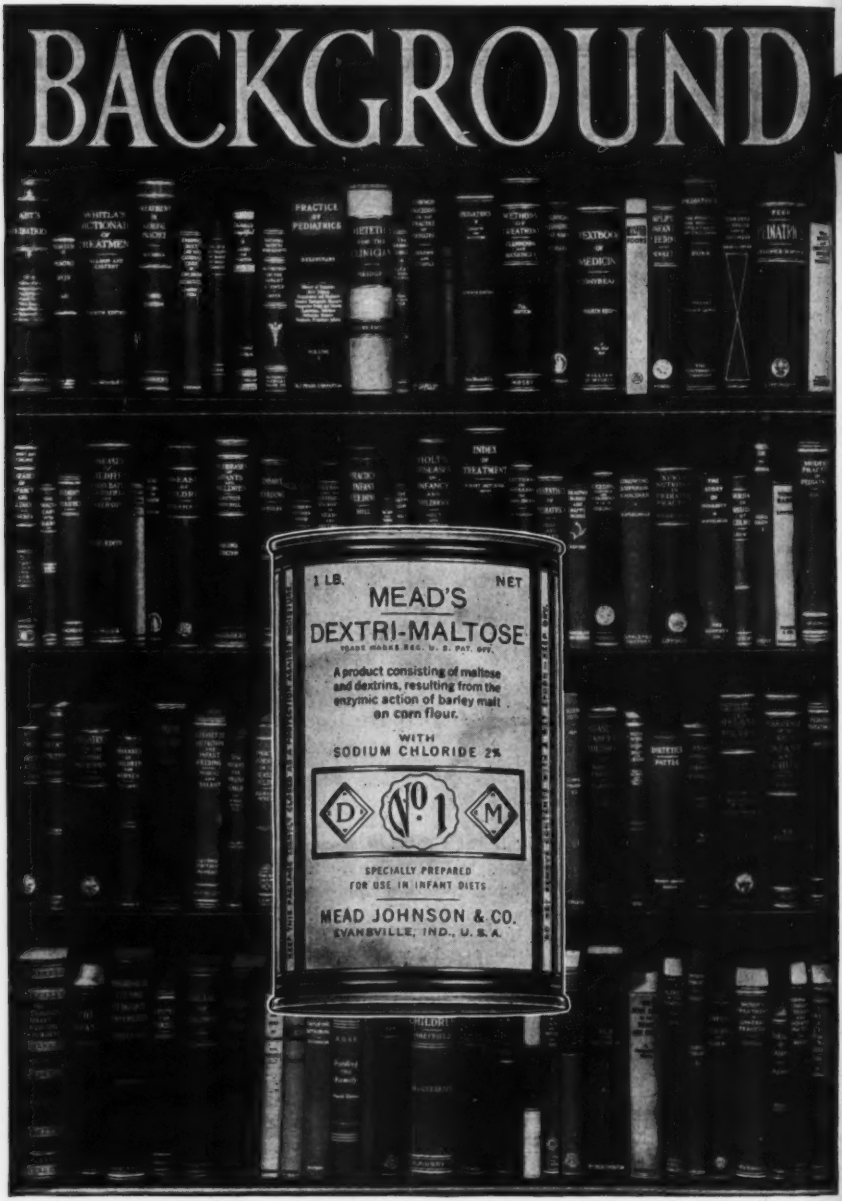
JUL 19 1962

BACKGROUND



THE use of cow's milk, water and carbohydrate mixtures represents the one system of infant feeding that consistently, for over three decade has received universal pediatric recognition. No carbohydrate employ in this system of infant feeding enjoys so rich and enduring a backgrou of authoritative clinical experience as Mead's Dextri-Maltose.